REMARKS

I. Introduction

This is in response to the Office Action dated July 25, 1995. A petition under 37 CFR §1.136 and the required fee requesting a three month extension in which to file this amendment was filed, along with the amendment for which this is a substitute, on January 25, 1995. With the extension, this response was due on January 25, 1996. No additional fees are believed to be necessary for the filing of this amendment, but if such fees are required, applicants request that this be considered a petition therefor, and the Commissioner is hereby authorized to charge any additional fees which may be required for the filing of this amendment to Deposit Account No. 11-1158.

The requirement for formal photographs and for a petition under 37 CFR 1.84(b) is noted. Such a petition will be submitted once allowable subject matter has been agreed upon, if not sooner. Replacement photographs will be submitted when such a petition has been granted, if not sooner.

II. Title

As requested by the Examiner, the title of the invention has been amended in order to clearly indicate that the invention to which the claims are directed involves "the use of antibodies specific to human complement component

DUPLICATE

C5". Support for this change may be found, for example, on page 1, line 10 of applicants' specification.

III. **The §112 ¶1 Rejections**

The Examiner has objected to the specification and rejected claims 1-6 under 35 U.S.C. §112, first paragraph, for "insufficient evidence or nexus with respect to in vivo operability of C5-specific antibodies". Applicants are puzzled by the Examiner's assertion that Examples 1-4 disclose extracorporeal treatment only. While Examples 1-4 of copending US patent application Serial No. 08/217,391, filed March 23, 1994, which is cited in the instant specification, do disclose extracorporeal treatment only, examples 1-3 of the instant application disclose only *in vivo* treatment, and examples 4-6 disclose both *in* vivo and extracorporeal treatment data. Clarification is respectfully requested.

The Examiner asserts that pharmaceutical therapies in the absence of *in vivo* clinical data are unpredictable. Applicants note that they have provided evidence of *in vivo* operability in a mouse model of glomerulonephritis in their specification. Nonetheless, a "Declaration of Louis A. Matis Pursuant to 37 C.F.R. §1.132", which sets forth, *inter alia*, experimental data that further demonstrate the operability of applicants' invention, is being submitted herewith.

In addition, with regard to the pharmacokinetics of monoclonal antibodies in general, the Harris et al.

reference cited by the Examiner (Examiner's reference R1) indicates at page 42, column 3, that murine antibodies generally have *in vivo* half-lives on the order of 15 hours, and that chimeric antibodies have even longer half-lives *in vivo*, on the order of 100 hours. Moreover, rodent monoclonal antibodies in general have been shown to be non-toxic in clinical use, and Harris et al. state that "an important conclusion, drawn from all the available data, is that chimaeric antibodies are non-toxic." (Harris et al., p. 42, column 3). Finally, the Declaration of Scott A. Rollins Pursuant to 37 C.F.R. §1.132, submitted herewith, sets forth data obtained *in vivo* in a rhesus monkey demonstrating that the N19-8 antibody used in the examples of applicants' specification provides effective complement inhibition with a functional half life of approximately 24 hours, and without adverse reactions.

The Examiner has disparaged antibody therapy based on the Harris et al. reference. The key assertion by Harris et al. cited by the Examiner in this regard is that repeated dosing with chimeric antibodies is ineffective due to anti-idiotypic responses. This assertion is belied by the actual *in* vivo human data currently available, as exemplified by the recent FDA approval and successful marketing of the chimeric monoclonal antibody antithrombotic agent REOPRO, which, unlike the other currently marketed monoclonal antibody, OKT3, is not an immunosuppressive agent and is not typically used in immunosuppressed patients. Furthermore,

the mouse animal model study data set forth in applicants' specification and in the Declaration of Louis A. Matis Pursuant to 37 C.F.R. §1.132 (submitted herewith) demonstrate that the therapeutic benefit of antibody administration in accordance with applicants' teachings is seen following prolonged antibody administration, indicating that anti-idiotypic antibody production, if any, is insufficient to limit the therapeutic benefit of the methods of applicants' invention. Since the human response to humanized mAbs should parallel the murine response to murine mAbs, these data indicate that such anti-idiotype responses would not be expected to occur in human patients to an extent that would inhibit the therapeutic benefit of the methods of the present invention.

The Examiner also avers that

> [t]he specification does not adequately teach how to effectively inhibit the disease/treatment endpoint in humans by administering an inhibiting monoclonal antibody. The specification does not teach how to extrapolate data obtained from these controlled conditions evaluating extracorporeal treatment with C5/C5b-specific antibodies to the development of effective in vivo human therapeutic methods which are directed toward a chronic ongoing disease.

In fact, the procedures for administering the therapeutic antibodies used in the process of the invention and monitoring their effects are fully set forth in applicants' specification (see, for example, pages 25-28). The guidance for the development of effective in vivo human therapeutic methods provided in applicants' specification is

not limited to the controlled conditions evaluating extracorporeal treatment mentioned by the Examiner. As discussed above, applicants' specification also provides working examples demonstrating the practice of their invention via effective *in vivo* therapeutic methods in a widely used animal model of glomerulonephritis.

The conclusions of the above discussions regarding the practice of the invention in human patients *in vivo* are supported and extended by the Declaration of Bernadette L. Alford Pursuant to 37 C.F.R. §1.132, which is being submitted herewith.

The Examiner has also asserted that it is unclear whether the antibodies used in the practice of the invention would be neutralized by the patient's complement found in the circulation. The *in vivo* data of the specification, as well as data of the declarations submitted herewith, including the Declaration of Louis A. Matis Pursuant to 37 C.F.R. §1.132, discussed above, and the Declaration of Scott A. Rollins Pursuant to 37 C.F.R. §1.132, clearly show that if any such neutralization does occur, it is sufficient neither to markedly decrease complement inhibition nor to render the methods of the invention inoperative.

With regard to therapeutic complement inhibitors in general, the Examiner has cited Liszewski et al. (Examiner's reference S3), Morgan (Examiner's reference S4), and Kalli et al. (Examiner's reference T5). It appears that the

Examiner's discussion of these references is colored by the misapprehension that no *in vivo* evidence of operability is presented in applicants' specification. As discussed above, this is not the case.

In the Examiner's argument contending that applicants' claims are not adequately enabled by their specification, Morgan (Examiner's reference S4) is cited as indicating that long term complement inhibition could leave the recipient susceptible to infections (see Morgan, p. 225 column 1, final paragraph). In this regard, applicants draw the Examiner's attention to the sentence immediately following the cited sentence in the referenced paragraph, which reads: "These problems pose a challenge to clinicians, but are unlikely to restrict our use of these exciting new agents."

Morgan's comments regarding infections were made in the context of his discussion of sCR1 in the preceding sentences of the referenced paragraph. As discussed at page 12, line 23, to page 13, line 8 of applicants' specification, lack of C3 function (as occurs with sCR1 treatment) leaves patients prone to a broad variety of infections, while lack of C5 function (as occurs in association with the practice of the present invention) only has a minor effect on susceptibility to infection, and then only to Neisseria infection. This represents a distinct advantage of applicants' invention over prior art approaches to therapeutic complement inhibition.

Applicants believe that the preceding discussion fully addresses the Examiner's concerns, and respectfully request that the Examiner reconsider and withdraw his rejections under §112, paragraph 1.

IV. The §112 ¶2 Rejections

The Examiner has rejected claims 1-8 under 35 U.S.C. §112, second paragraph, as being indefinite for a combination of reasons including (A) indefiniteness in the recitation of an antibody that "binds to" and an antibody "to" (claims 1-8); (B) indefiniteness "in the recitation of a 'pharmaceutical agent' because it is unclear whether applicant is claiming a compound or composition" (claims 6-9); and (D) duplicative claiming (claims 7-9).

Regarding reason (A), claim 1 has been amended in accordance with the Examiner's suggestion to recite an antibody " specific to" C5. Support for this change can be found (*inter alia*) at page 1, line 10 of applicants' specification. Claims 2-5 depend on Claim 1, and are thus also corrected by the language of this amendment.

Regarding reason (B), claims 6-9 recite an "article of manufacture" and thus are directed neither at a compound nor a composition *per se*, but at a "manufacture" in accordance with 35 U.S.C. §101. Applicants respectfully traverse the Examiner's assertion that the claims read on a composition *per se*. Nonetheless, in the interest of expediting

prosecution, applicants have hereby canceled claims 6-9 without prejudice to their use in a continuing application.

Regarding reason (C), as discussed in the preceding paragraph, claims 6-9 were directed to articles of manufacture, not compositions. The articles of manufacture of claims 6-9 comprise combinations of packaging materials and formulations, and are distinguished from each other by the indicia of the label portion of the packaging material. Applicants therefore respectfully traverse the Examiner's assertion that claims 7 and 8 are essentially duplicative of claim 6. Nonetheless, as discussed above, applicants have hereby canceled claims 6-9 without prejudice.

Applicants believe that the preceding discussion fully addresses the Examiner's concerns, and respectfully request that the Examiner reconsider and withdraw his rejections under §112, paragraph 2.

V. The §103 Rejections

In the July 25th Office Action, the Examiner rejected applicant's pending claims 1-5 under 35 U.S.C. §103 over Wurzner et al. (Complement Inflamm., 1991; 1449 #20) in view of Couser et al. (J. AM. Soc. Nephrol., 1991, 1449 #5) and Sims et al. (U.S. Patent No. 5,135,916 1449 #1). Applicants respectfully traverse these rejections, as well as the rejections of claims 6-9 (hereby canceled) over Wurzner et al. (Complement Inflamm., 1991; 1449 #20).

Applicants' traversal of these rejections is based upon several arguments, including the following:

1. As discussed in applicants' specification, page 23, lines 6-16, and discussed more fully in the Declaration of Louis A. Matis Pursuant to 37 C.F.R. §1.132, submitted herewith, it would be counterintuitive to treat a disease process that involves inordinately high levels of circulating antibody-antigen immune complexes, resulting in immune complex deposition in the kidneys, with a treatment that is almost certain to result in the generation of more circulating antibody-antigen immune complexes, and thus increase the already pathologically high levels of such complexes in the circulation.

   Furthermore, Kalli et al. (Examiner's reference T5) teach away from applicants' invention. Kalli et al. recite criteria that they claim must be met in order for complement inhibitors to be effective therapeutic agents. Since the mAbs used in the methods of the present invention do not meet these criteria, Kalli et al would suggest that, contrary to the experimental results set forth in the examples of applicants' specification and those of the Declarations submitted herewith, these mAbs would not make effective therapeutic agents.

2. As discussed in the Declaration of Louis A. Matis Pursuant to 37 C.F.R. §1.132 (submitted herewith) the prior art would have suggested that complement inhibition

alone would not be effective blocking or treating glomerular inflammation because of the large number of other proinflammatory agents believed to contribute to glomerular inflammation in this disease.

3. Even if the methods of applicants' invention would have been obvious to try (and applicants submit that the above arguments demonstrate that they would not have been) a practitioner of ordinary skill in the art would not have had a reasonable expectation of success in practicing the methods of the present invention, both due to the reasons discussed the arguments above, and because of other reasons arising from the level of understanding in the art at the time the invention was made.

For example, as the Examiner has pointed out, various potential problems made the outcome of experiments testing the efficacy of the methods of the present invention uncertain. (Although, as discussed above, the data presented in the examples of applicants' specification and in the Declarations submitted herewith demonstrate that the methods of their invention are indeed successful.) These potential problems highlighted by the Examiner include uncertainty regarding "specificity, binding constants, tissue penetration, clearance rates, and mode of action of the effector" as well as overly short half life (e.g., due to inactivation by proteases), and inability to reach the target area.

The Examiner's recognition of these potential problems clearly demonstrates that, even if applicants' methods were obvious to try (which, applicants argue, was not the case -- see above) their methods can not properly be construed as having had that essential criterion for obviousness under §103, a reasonable expectation of success.

4. There has been a long felt but unmet need in the art for methods such as those of the present invention. See Liszewski et al. (Examiner's reference S3, first full paragraph of page 933) "Because complement can mediate cell and tissue damage in autoimmune syndromes, the possibility of harnessing its inhibitors to prevent undesirable activation has been a longstanding goal. At the present time there are no inhibitors of complement activation utilized in clinical medicine."

In this regard, applicants note that the all of the references cited by the Examiner were published in 1991. Thus, several years elapsed between the time that these references became available and the filing date of the instant application, during which time, and in spite of the disclosures of those references and the long felt and unmet need in the art, no other practitioners reported attempts to use antibodies against C5 (or any other terminal complement component) as therapeutic agents for the treatment of kidney disease.

Applicants submit that this lack of attempts to use anti complement antibodies to treat glomerulonephritis prior to their invention demonstrates that the use of any of these antibodies (and in particular the specific use of anti C5 antibodies) to treat this predominantly immune complex mediated disease was counterintuitive, and hence nonobvious.

In sum, applicants believe that their amended claims fully satisfy the requirements of section 103 of the Patent Statute. Applicants therefore respectfully request that the Examiner reconsider and withdraw his rejections under §103.

VI. Conclusion

In view of the foregoing, applicants respectfully submit that the present application is in condition for allowance. Accordingly, reconsideration and the issuance of a notice of allowance for this application are respectfully requested.

Respectfully submitted,

Date: April 15, 1996

Seth A. Fidel, Ph.D.
Reg. No. 38,449
Alexion Pharmaceuticals, Inc.
25 Science Park, Suite 360
New Haven, CT 06511